Brief Report

Haplotypes of Transcription Factor 7–Like 2 (*TCF7L2*) Gene and Its Upstream Region Are Associated With Type 2 Diabetes and Age of Onset in Mexican Americans

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TCF7L2 **acts as both a repressor and transactivator of genes, as directed by the Wnt signaling pathway. Recently, several highly correlated sequence variants located within a haplotype block of the *TCF7L2* gene were observed to associate with type 2 diabetes in three Caucasian cohorts. We previously reported linkage of type 2 diabetes in the San Antonio Family Diabetes Study (SAFADS) cohort consisting of extended pedigrees of Mexican Americans to the region of chromosome 10q harboring *TCF7L2*. We therefore genotyped 11 single nucleotide polymorphisms (SNPs) from nine haplotype blocks across the gene in 545 SAFADS subjects (178 diabetic) to investigate their role in diabetes pathogenesis. We observed nominal association between four SNPs (rs10885390, rs7903146, rs12255372, and rs3814573) in three haplotype blocks and type 2 diabetes, age at diagnosis, and 2-h glucose levels ($P = 0.001–0.055$). Furthermore, we identified a common protective haplotype defined by these four SNPs that was significantly associated with type 2 diabetes and age at diagnosis ($P = 4.2 \times 10^{-5}$, relative risk [RR] 0.69; $P = 6.7 \times 10^{-6}$, respectively) and a haplotype that confers diabetes risk that contains the rare alleles at SNPs rs10885390 and rs12255372 ($P = 0.02$, RR 1.64). These data provide evidence that variation in the *TCF7L2* genomic region may affect risk for type 2 diabetes in Mexican Americans, but the attributable risk may be lower than in Caucasian populations. *Diabetes* 56:389–393, 2007**

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Recently, a DNA sequence variant of the transcription factor 7–like 2 (*TCF7L2*, formerly *TCF4*) gene has been found to be significantly associated with type 2 diabetes in an Icelandic case-control study. This finding has been replicated in two other Caucasian case-control cohorts from Denmark and the U.S. (1). Interestingly, *TCF7L2* has been shown to mediate regulation of glucagon-like peptide-1 expression (2), and this may be a mechanism by which alteration of this gene influences susceptibility to type 2 diabetes. The variant of *TCF7L2* that has been observed to be associated with type 2 diabetes is a microsatellite marker (DG10S478) located in intron 3 (1). Additionally, the genotypes of five single nucleotide polymorphisms (SNPs) within the same large haplotype block that were correlated with DG10S478 were also associated with type 2 diabetes. The authors recommended that the two most highly correlated SNPs, rs12255372 and rs7903146, be included in replication attempts. Subsequently, these two SNPs have been associated with type 2 diabetes and impaired glucose tolerance in an Amish population and with measures of insulin sensitivity and insulin secretion in non-Amish, nondiabetic subjects (3). In addition, among participants of the Diabetes Prevention Program, TT homozygotes at these two SNPs were more likely to progress from impaired glucose tolerance to type 2 diabetes than noncarriers of the SNPs (4). We previously reported significant linkage of type 2 diabetes and its age of onset in the San Antonio Family Diabetes Study (SAFADS) cohort of Mexican-American pedigrees to the region of chromosome 10q harboring *TCF7L2* (5). We therefore genotyped the two recommended SNPs (rs7903146 and rs12255372) and nine others from nine haplotype blocks across the gene in SAFADS subjects in order to investigate whether these variants were associated with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study subjects and phenotype definitions. Subjects used in this study were participants of the SAFADS, which consists of extended pedigrees and has been described in detail elsewhere (5). Probands for SAFADS were low-income Mexican Americans with type 2 diabetes, and all first-, second-, and third-degree relatives of the probands, aged ≥18 years, were considered eligible for the study. The baseline SAFADS exam consisted of 579 subjects distributed across 32 families. The cohort is 41% male, 32.7% had diabetes, and mean age of diabetes diagnosis was 48.4 ± 13.3 years. Genomic DNA was available for 545 subjects for this study. Diabetes was defined by having either a fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or a 2-h glucose level

following an oral glucose tolerance test ≥11.1 mmol/l (200 mg/dl) (6). Participants who did not meet these criteria but who self-reported physician-diagnosed diabetes and who reported current therapy with either oral antidiabetic agents or insulin were also considered to have diabetes. The institutional review board of the University of Texas Health Science Center at San Antonio approved all procedures, and all subjects gave informed consent.

SNP genotyping. For selection of SNPS, the program Haploview (7) was used to conduct linkage disequilibrium and haplotype block analyses using HapMap (8) Phase II genotype data for the chromosomal region 10:114581000–114914000 (HapMap release 20 [Jan. 2006]). Since genotypes representing Hispanic populations are not available, Centre d'Etude du Polymorphisme Humain (CEPH) Utah (CEU) genotypic information was used. This preliminary analysis indicated that for the 140 SNPs with minor allele frequency ≥5%, capturing 100% of alleles with $r^2 > 0.8$ across this expanse of 333 kb requires genotyping a minimum of 62 SNPs. For this study, SNPs were selected from nine haplotype blocks across this region for analysis. In addition, for replicative purposes, SNPs rs7903146 and rs12255372 were included. Using these 11 SNPs (and $r^2 > 0.8$), we were able to capture ~40% (56 SNPs) of the HapMap phase II CEU common variation in *TCF7L2*. Genotyping of all SNPs was completed using the Applied Biosystems (Foster City CA) TaqMan Allelic Discrimination methodology on an ABI Prism 7900HT Sequence Detection System according to the manufacturer's instructions. The discrepancy rate of duplicate genotyping was <0.2%, and the call rate was 99%. Further, no Mendelian inconsistencies were observed.

Statistical analyses. The analyses were conducted using variance components-based methods. To analyze type 2 diabetes as a discrete phenotype in the variance components framework, we used the threshold model described by Duggirala et al. (5,9). The threshold model assumes that an individual belongs to a specific disease category if an underlying genetically determined risk or liability exceeds a certain threshold on a normally distributed liability curve. The liability is assumed to have an underlying multivariate normal distribution. To corroborate the results of the discrete trait analysis, we also included two quantitative variables closely related to diabetes: 2-h glucose levels and the age of diabetes diagnosis. SAS was used to model age of diabetes diagnosis as a proxy for age of diabetes onset by using a Cox proportional hazards model (10). In the Cox proportional hazards model, for previously diagnosed diabetic participants, self-reported age of diagnosis was used as the time of the event; for diabetic subjects initially diagnosed at the SAFADS examination, the participants' reported age at that examination was used as the time of the event; nondiabetic participants were censored at their SAFADS examination age. The Martingale residual from the Cox proportional hazards model, a quantitative trait, was used in the subsequent genetic analyses (11,12). Since the SAFADS families were ascertained on the basis of type 2 diabetic probands, our analyses included ascertainment correction (13).

Linkage disequilibrium between each pair of SNPs was calculated by direct correlation (r^2) between SNP genotype vectors in which individual SNP genotypes were scored as 0, 1, or 2, depending upon how many copies of the rarer allele an individual carried. Haplotypes were estimated using the computer program SimWalk2 (14). Haplotype score vectors were then generated with elements containing a 0, 1, or 2, depending upon the number of copies of a specific haplotype that an individual carried.

To test the association between each SNP or haplotype and the phenotypic traits, a measured genotype approach (15) was used, which accounts for the relatedness among family members by estimating the likelihood of genetic models given the pedigree structure. Using a fixed effect model to code for the observed number of an allele (or haplotype) carried by an individual (i.e., 0, 1, or 2 copies), and assuming an additive model of allelic action, we tested whether the phenotypic means (or risk of disease) of study participants varies as a function of "allelic dosage." To account for the nonindependence of related individuals, a variance component was included that accounts for the overall genetic similarity between all pairs of individuals (based on their relationship coefficients) and for the genetic similarity in the region of interest (based on computed allelic sharing probabilities computed from observed marker genotypes in the region). Within each model, we simultaneously estimated the effects of age and sex. The measured genotype method was implemented by using SOLAR (16) as described previously (11). The relative risks (RRs) are the ratios of the mean genotype-specific liabilities for individuals carrying either one or two copies of the rare allele versus the mean liability for individuals carrying two copies of the common allele. To address possibilities of hidden population stratification in the SAFADS population, we used a pedigree test of transmission disequilibrium, specifically the quantitative trait disequilibrium test as described by Abecasis et al. (17). The model of Abecasis et al. (17) is used to partition the total association into within (β_w) and between (β_b) family components, using allelic transmission scores in extended pedigrees. The parameters β_w and β_b are modeled as the fixed effects within a variance components framework. Given that β_b could be confounded by population stratification, this approach is used to address the issue of population stratification by testing whether $\beta_b = \beta_w$. In the absence of population stratification, $\beta_b = \beta_w$.

To assess whether *TCF7L2* SNPs account for the linkage signal, linkage on chromosome 10 was reevaluated conditional to the measured genotype (i.e., SNP or haplotype) effects. This method and background have been described by Almasy and Blangero (18) and by Boerwinkle et al. (15). If the measured genotype is the sole functional variant in this region of linkage, then identity-by-descent allele sharing should provide no additional information, and the logarithm of odds score in the conditional linkage analysis is expected to drop substantially.

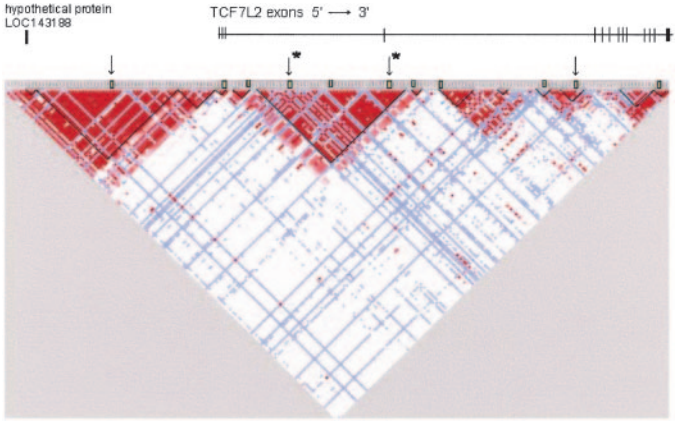

FIG. 1. Plot of linkage disequilibrium (AbsD′ measure) determined by the program Haploview using genotypic information from Phase II of the International HapMap project for CEU samples (HapMap release 20 [Jan. 2006]) in the chromosomal region 10:114581000–114914000. The approximate locations of the TCF7L2 exons are indicated as tick marks above the plot. The 11 SNPs genotyped in this study are boxed. The four SNPs exhibiting associations with diabetes traits are marked with an arrow. The two SNPS associated with increased risk for type 2 diabetes in Grant et al. (2) are also marked with an asterisk.

RESULTS AND DISCUSSION

We genotyped 11 SNPs selected from nine haplotype blocks across the *TCF7L2* gene region. The approximate locations within the genomic sequence are shown in Fig. 1, and the pairwise correlations among these SNPs in this Mexican-American population are shown in Fig. 2*A*. Our estimate of linkage disequilibrium structure in this population is consistent with that generated in the CEU HapMap samples, as shown in Fig. 2*B*. The characteristics of each SNP are also shown in Table 1. The allele frequencies for all SNPs except rs10885390 were consistent with CEU population. The minor allele frequency for rs10885390 was lower in the Mexican-American subjects of SAFADS (18%) than in CEU (28%). No SNPs deviated from Hardy-Weinberg expectations.

Table 1 summarizes the results of genotypic association analyses using an additive model for each SNP. Nominal association ($P = 0.001–0.055$) with type 2 diabetes and the related quantitative traits age of diagnosis and 2-h glucose level was observed for four SNPs. Association with type 2 diabetes and SNPs rs7903146 and rs12255372, the two SNPs reported to be highly correlated with marker DG10S478 in Caucasian populations (1), was observed at $P = 0.030$ and 0.033, respectively. The minor alleles (T) for both SNPs were associated with increased risk for type 2 diabetes, which is consistent with Grant et al. (1), although the point estimates for RRs are substantially less in this population (Table 1) compared with those reported for the Caucasian populations. In addition, both SNPs were associated with increased 2-h glucose levels (rs7903146 $P = 0.004$ and rs12255372 $P = 0.002$) but only approached

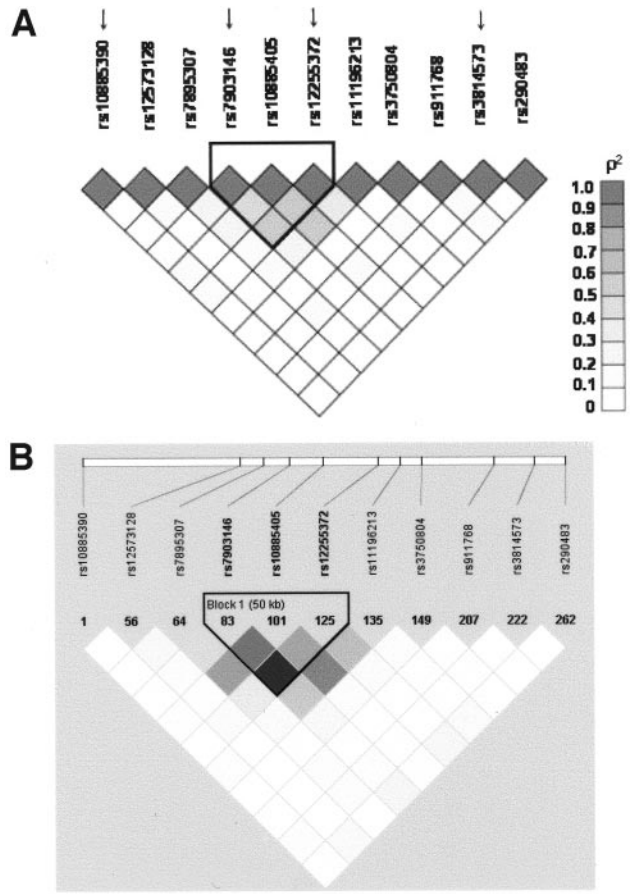

FIG. 2. Pairwise linkage disequilibrium among 11 SNPs characterized within *TCF7L2* gene. *A*: The SAFADS population. Figure depicts the measure r^2 between pairs of SNPs by intensity of shaded box as shown in the key. The uppermost row represents a comparison of each SNP against itself (i.e., $r^2 = 1.0$). The four SNPs exhibiting associations with diabetes traits are marked with an arrow. For orientation purposes only, the haplotype block containing SNPs rs7903146 to rs12255372 is indicated. *B*: The CEU samples (HapMap release 20 [Jan. 2006]). Figure depicts r^2 in which a decrease in r^2 is shown by decrease in shading intensity. Figure differs from *A* in that the uppermost row representing a comparison of each SNP against itself is not shown.

nominal significance for age at diagnosis ($P = 0.055$). Another SNP, rs10885390, which is located in another large haplotype block upstream of *TCF7L2* exon 1, exhibited a similar pattern and slightly stronger association with all traits ($P = 0.002$ for type 2 diabetes, $P = 0.014$ for age at diagnosis, and $P = 0.001$ for 2-h glucose). The SNP rs3814573 located in intron 4 was also associated with all traits ($P = 0.012$ for type 2 diabetes, $P = 0.0003$ for age at diagnosis, and $P = 0.010$ for 2-h glucose). When only the type 2 diabetes case subjects ($n = 178$) were included in the age-of-diagnosis analysis, only SNP rs3814573 remained associated ($P = 0.005$). We also tested for association with fasting and 2-h insulin measures as well as fasting and 2-h glucose measures among nondiabetic subjects only ($n = 367$). No SNPs were associated with either insulin trait. Additionally, only SNP rs12255372 approached nominal significance for association with 2-h glucose values among nondiabetic subjects ($P = 0.055$). Further, no evidence for hidden population stratification (i.e., admixture) was observed using the quantitative trait disequilibrium test for each trait of interest ($P = 0.25$–0.95).

We conducted haplotype analyses using the four associated SNPs. Fifteen haplotypes were observed in this population, ranging in frequency from 40 to 0.12%. As shown in Table 2, in which the risk alleles are underlined, the mere absence of the risk alleles of SNPs rs790314 or rs1225532 did not confer protection from diabetes. The most common haplotype lacked both of the risk alleles at these positions but was not associated with diabetes, age of onset, or 2-h glucose values. However, another common haplotype (hap 2 in Table 2) lacking the risk alleles for all four associated SNPs (boldface in Table 1) displayed strong evidence for protection against type 2 diabetes ($P = 4.2 \times 10^{-5}$, RR 0.69), a higher age at diabetes diagnosis ($P = 6.7 \times 10^{-6}$), and lower 2-h glucose values ($P = 1.5 \times 10^{-4}$). The risk allele T of SNP rs12255372 was present on seven different haplotypes in this population, ranging in frequency from 0.4 to 6.8%, and only conferred increased risk for diabetes when the minor allele A of upstream SNP rs10885390 was also present (i.e., haplotypes 4, 8, and 11). The RR for carrying one or any combination of two copies

TABLE 1
Association analyses results and characteristics of individual SNPs in the TCF7L2 gene region in the SAFADS

						Type 2 diabetes		Age at diagnosis		Nondiabetic subjects only	
NCBI dbSNP ID	Chromosome 10 locus	LOC in TCF7L2	Major/ minor allele	MAF	2-h glucose (*P*)	*P*	RR (1 copy/ 2 copies)*	*P*	Effect on age†	2-h glucose (*P*)	2-h insulin (*P*)
rs10885390	114630787	**5′ to gene**	T/A	**0.18**	**0.001**	**0.002**	**1.15/1.44**	**0.014**	**Decrease**	0.251	0.230
rs12573128	114720787	Intron 3	A/G	0.28	0.285	0.055	0.92/0.90	0.039		717	0.616
rs7895307	114733951	Intron 3	G/A	0.48	0.864	0.525	1.02/1.04	0.784		0.784	0.357
rs7903146‡	114748339	**Intron 3**	C/T	**0.23**	**0.004**	**0.030**	**1.09/1.24**	0.055	Decrease	0.376	0.238
rs10885405	114767660	Intron 3	C/T	0.30	0.056	0.275	1.04/1.09	0.378		0.258	0.424
rs12255372‡	114798892	**Intron 4**	G/T	**0.21**	**0.002**	**0.033**	**1.08/1.21**	0.055	Decrease	0.055	0.939
rs11196213	114811544	Intron 4	C/T	0.28	0.204	0.512	1.02/1.05	0.551		0.612	0.050
rs3750804	114823840	Intron 4	C/T	0.22	0.643	0.744	0.99/0.97	0.266		0.241	0.150
rs911768	114864761	Intron 4	G/C	0.29	0.351	0.041	1.07/1.18	0.106		0.475	0.850
rs3814573	114888083	**Intron 4**	C/T	**0.31**	**0.010**	**0.012**	**0.91/0.86**	**3×10^{-4}**	**Increase**	0.401	0.380
rs290483	114905204	Intron 10	T/G	0.36	0.693	0.847	0.99/0.99	0.394		0.395	0.750

*RR when bearing one or two copies of minor allele vs. risk for being homozygous for major allele when using an additive model. †"Decrease" means age at onset is lower in carriers of minor allele than in subjects homozygous for major allele. ‡SNPs in linkage disequilibrium with DGS10S478 and associated with diabetes in a Caucasian population (1). Common haplotypes lacking the risk alleles for all four associated SNPs are shown in boldface. LOC, location; MAF, minor allele frequency.

TABLE 2
Results of association analyses of haplotypes for the TCF7L2 locus in SAFADS subjects.

Hap.*	rs10885539†	rs7903146†	rs12255372†	rs3814573†	Freq.	2-h glucose	Type 2 diabetes		Age at diagnosis		Nondiabetic subjects only	
							P	RR (1 copy/ 2 copies)†	*P*	Effect on age§	2-h glucose (*P*)	2-h insulin (*P*)
1	T	C	G	C	0.399	0.973	0.468	1.02/1.05	0.196		0.480	0.766
2	**T**	**C**	**G**	**T**	0.261	**1.5×10^{-4}**	**4.2×10^{-5}**	**0.78/0.69**	**6.72×10^{-6}**	**Increase**	0.170	0.746
3	T	T	T	C	0.068	0.391	0.874	1.01/1.02	0.968		0.190	0.480
4	A	T	T	C	0.054	**0.006**	**0.024**	**1.20/1.64**	**0.017**	**Decrease**	0.194	0.789
5	A	C	G	C	0.046	0.286	0.463	1.06/1.13	0.400		0.258	0.861
6	T	T	G	C	0.039	0.179	0.507	1.08/1.20	0.046		0.723	0.699
7	T	T	T	T	0.032	0.612	0.858	0.98/np	0.584		0.776	0.242
8	A	C	T	C	0.021	0.126	0.081	1.33/np	**0.042**	**Decrease**	0.880	0.550
9	A	T	G	C	0.020	0.994	0.662	0.94/np	0.173		0.435	0.446
10	A	C	G	T	0.015	0.478	0.132	1.34/np	0.417		0.416	0.155
11	A	T	T	**T**	0.012	0.069	**0.026**	**2.07/np**	0.356		0.188	0.371
12	T	C	T	C	0.011	0.270	0.033	0.76/np	0.164		0.399	0.582
13	T	T	G	T	0.009	0.642	0.735	1.06/np	0.866		0.524	0.157
14	T	C	T	T	0.004	1.000	0.577	0.82/np	0.860		0.998	0.560
15	A	T	G	T	0.001	0.460	0.992	0.83/np	0.996		0.204	0.134

*Observed haplotypes numbered by decreasing frequency. †SNP allele associated with conferring increased risk for type 2 diabetes (as shown in Table 1) is underlined. ‡RR of carrying either one or two copies of the haplotype vs. risk for not bearing the haplotype; np indicates that two copies of this haplotype were not present in any subject of the SAFADS. §"Decrease" means age at onset is lower in subjects bearing two copies of the haplotype than in subjects not carrying haplotype. Common haplotypes lacking the risk alleles for all four associated SNPs are shown in boldface.

of these uncommon haplotypes was 1.23 and 1.79, respectively, when using an additive model.

To determine whether genotypes at this locus accounted for our 10q linkage signal, we conducted linkage analysis conditional to a measured genotype for the individual SNPs and the haplotypes. As in the Icelandic population, neither of their associated SNPs (rs7903146 or rs1225372) accounted for the linkage in the SAFADS. Also, SNP rs10885390, by itself, did not account for any part of the 10q linkage signal. We observed the linkage signal to be affected by genotypes at SNP rs3814573, which accounted for ~9% of the diabetes signal. The effect of the minor allele for this SNP appears to be protective. Furthermore, the haplotype bearing all protective alleles (hap 2, described above) accounts for ~15% of the linkage signal. No risk haplotypes appear to account for the linkage signal.

In summary, we observed a nominal association between SNPs in *TCF7L2* and type 2 diabetes in a cohort of Mexican-American families. These SNPs include two located in introns 3 and 4 that were previously shown to be associated with increased risk in Caucasian populations (1,3,4), one that is located in another large haplotype block immediately upstream of *TCF7L2*, and another SNP located further downstream in intron 4 (rs3814573). These results provide replicating evidence for the TCF7L2 variants proposed by Grant et al. (1) and suggest that there are additional variants of the *TCF7L2* gene that affect type 2 diabetes susceptibility. Conversely, our data provide additional evidence for a potential role for alterations in the *TCF7L2* gene in type 2 diabetes pathogenesis but indicate that the causal *TCF7L2* variant has not been identified to date.

Our analyses of glucose and insulin levels among the nondiabetic subjects do not indicate any significant effect of these SNPs on these levels. It is possible that the magnitude of the effect is too small to detect in the smaller sample. This is consistent with our lower point estimates of diabetes RR in this population, suggesting that the attributable risk among Mexican Americans may not be as high as that reported in Caucasian populations. It is likely that other unidentified variants within this large gene are the true functional sites, at least in this population. This possibility is reinforced by the fact that the SAFADS 10q linkage signal is not fully accounted for by these *TCF7L2* SNPs. Moreover, we have identified haplotypes in the SAFADS that are either more strongly associated with type 2 diabetes and its related quantitative measures or confer much greater risk than that attributed to the single SNPs in this population. This suggests that a variant present on these haplotypes is the true functional site. In addition to the risk haplotypes bearing the minor alleles at SNPs rs10885390 and rs12255372, we have also observed evidence for a common protective haplotype bearing the minor allele at SNP rs3814573 located in intron 4. This haplotype may bear a protective variant(s) of *TCF7L2* or conversely may represent a subset of individuals who do not bear the as-yet-unidentified risk variant. Its high frequency in the population may be the reason that observed associations are the most significant. Further evaluation of this gene, and importantly its upstream region, may elucidate the causal variant(s) in this and other populations.

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